REVIEW ARTICLE

The Economics of Biosimilars

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Background: The high cost of pharmaceuticals, especially biologics, has become an important issue in the battle to control healthcare costs. The Hatch-Waxman Act encourages generic competition but still provides incentives for pioneers to develop new drugs. The Biologics Price Competition and Innovation Act is intended to do the same for biologics and biosimilars.

Objective: To examine information related to biosimilars to determine their potential impact on competition in the biologic market.

Method: Using information concerning the European Union (EU) and the pharmaceutical industry, this article reviews and analyzes the experience of biosimilars in the EU, as well as the obstacles and opportunities that biosimilars face in the United States. Much of the analysis is based on examining current trends in biologic drugs and the potential implications on the future of biosimilars.

Discussion: This article reviews the mixed success of biosimilars in the EU and the implications for the United States. Because biologics are produced from living organisms, manufacturing issues are more important than in the chemical drug market. The barriers to biosimilar entry into the marketplace are much more difficult to overcome than challenges generic manufacturers typically face and are similar to obstacles specialty injectable producers encounter. The competitive responses by pioneers are also likely to be more important. The capital costs and risk issues with biosimilars make alliances and partnering arrangements very likely. Biosimilars often enter emerging markets, where the barriers to entry are easier to overcome. Nevertheless, the United States represents the greatest opportunity for biosimilar producers, in part because it is the largest biologics market and has high prices for biologics. As the United States enters the biosimilar market, the pharmaceutical industry is likely to grow at an accelerated pace. Automatic substitution is likely to be slow to develop, because of safety and quality concerns. The beneficial impact of biosimilars is likely to take a long time to be realized and to be fraught with more difficulties than was the case for small-molecule generics.

Conclusion: Various factors, such as safety, pricing, manufacturing, entry barriers, physician acceptance, and marketing, will make the biosimilar market develop different from the generic market. The high cost to enter the market and the size of the biologic drug market make entry attractive but risky.

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Am Health Drug Benefits. 2013;6(8):469-478
www.AHDBonline.com

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The high cost of pharmaceuticals, especially biologics, has become an important issue in the battle concerning ever-increasing healthcare costs. The average daily cost of a biologic in the United States is $45 compared with only $2 for chemical (small-molecule) drugs.[1] The Hatch-Waxman Act encourages generic competition but still provides incentives for pharmaceutical innovators to develop new drugs. The Biologics Price Competition and Innovation Act (BPCIA) of 2009 is intended to do the same for biologics and biosimilars. Now that the US Food and Drug Administration (FDA) can approve biosimilars, it is important to consider whether biosimilars are likely to have the same impact in the biologic drug market that generics have had in the chemical drug market.

The experience in the European Union (EU), where biosimilars were first marketed in 2007, is instructive. This article reviews the obstacles that biosimilar manufacturers face, as well as the opportunities, and evaluates the probable impact of biosimilars on the healthcare market. The potential impact of the BPCIA on prices and access in the biologic market are addressed.

Terminology and Definitions

The biologic market is composed of large-molecule drugs that are produced in living organisms. Biosimilars, unlike small-molecule generics, are not identical to the reference product. A biosimilar is "highly similar" to a branded drug, which is referred to as the "reference product."[2] The Affordable Care Act (ACA),

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KEY POINTS

- The high cost of pharmaceuticals, especially biologics, has an increasing impact on healthcare costs.
- Biosimilars have been available in the European Union since 2007 but are only now being considered for approval by the FDA.
- Biosimilars have the advantage of being able to extrapolate and "piggyback" on the branded drug to get approval for all the original drug's indications.
- The barriers to market entry for biosimilars are much more difficult to overcome than is typically seen with small-molecule generic drugs.
- Safety, pricing, manufacturing, market entry barriers, physician acceptance, and marketing will make the biosimilar market develop different from the generics market.
- As of mid-January 2013, the FDA received 13 inquiries about potential biosimilar application, but no applications have been filed.
- The first biosimilar marketed in the United States is likely several years away at least.
- Pharmaceutical alliances will be common, because of the need to share the risk inherent in biologic and biosimilar development; the possible extension of a patent for the original biologic is inherent in the risk of entering the biosimilar market.
- Large, well-established companies are expected to dominate that market.

which includes the BPCIA, defines biosimilars as having "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency."[2] The implementation of the ACA (the new healthcare law) requires many decisions by the FDA, such as the extent of clinical trials that will be required and developing guidelines for biosimilar entry.[2]

Because different countries have various regulatory requirements, the term "biosimilar" is often misused. Biosimilars that do not meet the requirements of being similar to the original drug are referred to as "noncomparable biologics." In this article we consider biosimilars to be those that were approved in the United States, EU, Canada, or Australia, and one should be cautious in referring to other countries' noncomparable drugs as biosimilars. Biobetters are biologics that exhibit superiority over the branded biologic in dimensions such as efficiency or clinical specificity.[2]

Biologics and Incentives for Innovation

The BPCIA recognizes the importance of encouraging innovation, but it also provides a pathway for competition once monopoly protection ends. Biologics can obtain patent protection, which lasts for 20 years from the date the patent application is filed.[3] Questions exist about the degree of protection afforded by biologic patents.[3] Accordingly, the BPCIA provides a 12-year market exclusivity and a 4-year data exclusivity beginning when the biologic drug receives FDA marketing approval. Each exclusivity can be extended 6 months for pediatric applications. A biosimilar cannot be marketed until the 12-year exclusivity expires.[3] These exclusivity protections are intended to encourage biologic research and development (R&D). Patents can be challenged in court, but exclusivity cannot.

There is often a lag of many years between patent approval and FDA approval to market a drug; therefore, a patent may run out before the exclusivity expires. By contrast, it is important that the data exclusivity expire before the market exclusivity, so that a biosimilar manufacturer can begin development work to ensure rapid market entry on the expiration of a biologic's market exclusivity. Furthermore, biosimilar entry would be encouraged by predictable approval requirements from the FDA and market acceptance, among other factors. This would decrease risk, leading to more entry and greater price discounting. The 12-year market exclusivity is a type of insurance policy, given the uncertainty of patent litigation, and is probably necessary to encourage innovation.

Biologics Market

The biologics market is growing rapidly, especially compared with the small-molecule chemical market whose revenues actually decreased in 2012. The future for many pharmaceutical firms is in biologics. Several biologics have sales of more than $1 billion annually. For example, in 2011, global sales were $7.19 billion for Remicade (infliximab) and $5.98 billion for Avastin (bevacizumab).[4] In addition, many of these very profitable drugs are scheduled to come off patent, providing the opportunity and incentive for biosimilar entry. Specifically, Herceptin (trastuzumab), Humalog (insulin lispro), Rituxan (and MabThera in Australia; rituximab), Remicade, and Aranesp (darbepoetin alfa) will lose patent protection within 5 years.[5] It is also estimated that 32 biologics, with a combined $51 billion of sales in 2009, will lose patent protection by 2015.[4] The opportunity exists, but unlike the generic market, where market entry is fairly simple and well established, there are substantial barriers to entry into the biosimilar market.

The investment needed to develop and market a biosimilar is considerably higher than the $1 million to $4

million that is required in the generic market. It takes 7 to 8 years to develop a biosimilar, at a cost of between $100 million and $250 million.[6] Moreover, the complexity of monoclonal antibodies makes their development and manufacturing costs much higher than for the biosimilars that are currently on the market in the EU. The US market is by far the largest and potentially most lucrative market for biosimilars. It has attracted the interest of various companies. At the same time, other companies have been discouraged by the lack of definitive standards for approval and the concerns about adequate profitability given the greater risk. In any event, biosimilar entry is probable only for the biologics with substantial sales and profits.

Table 1 Biosimilar Differences: European Union versus United States

Biosimilar parameters	European Union	United States
Exclusivity for first interchangeable drug	None	1 year
Regulatory application must show:	Efficacy and safety	Patient benefit
Decisions related to "biosimilarity" determined on case-by-case basis	Yes	Likely
Exclusivity period	10 years	12 years
Postmarketing requirements	Same as pioneer drug	Not yet determined

The EU Experience

The first biosimilar was approved in the EU in 2006.[7] However, although the EU market has grown over time, it is still relatively small. Only 16 biosimilars in 3 classes—human growth factor, short-acting erythropoietin, and daily granulocyte colony-stimulating factor (G-CSF)—have been approved. These 3 classes represent approximately 11% of the total patient volume and approximately 18% of all biologic sales.[7]

For the year ending June 2011, biosimilars accounted for approximately 10% of the available market, and biosimilars make up <1% of the total biologic sales in the EU.[7] However, the EU has approximately 80% of the global biosimilar market.[1] Long-acting erythropoietin and G-CSF are not included in the biosimilar market, because the patents have not expired for these products. Biosimilar prices in the EU have been on average approximately 30% less expensive than their reference products.[8]

In June 2013, Celltrion and Hospira received permission from the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use, and have recently received approval from the European Commission to market a biosimilar version of Johnson & Johnson's Remicade.[9] This is the first approval of a monoclonal antibody biosimilar. The biosimilar, called Remsima, will not be marketed in most of the EU until the EU patent for Remicade expires in February 2015, but it will be marketed in some countries in 2014. However, Johnson & Johnson has many secondary patents on Remicade and may file a patent infringement case to prevent the marketing of the biosimilars.[9]

EU countries generally prefer lower costs than increased access.[10] Automatic substitution at the pharmacy level has not occurred: the EMA advises against such substitution.[11] No European country (except Germany) has been willing to give preferential reimbursement treatment, which is important to long-term success.[10] In the EU, penetration rates for different biosimilars vary considerably between and within countries. In terms of companies, Sandoz has 3 biosimilars and has 50% of the total biosimilar market in the EU.[12] In the EU, the major players are large, well-established companies, such as Teva, Sandoz, and Hospira. One would expect the same to occur in the United States.

The experience of the EU does not particularly bode well for the initial success of biosimilars in the United States. The lack of automatic substitutability, the relatively small price savings, and the reluctance of physicians to use biosimilars explains the situation (**Table 1**).

Nevertheless, biosimilars have not had substantial safety issues in the EU. Despite the lack of safety problems in the EU, the United States is likely to err on the side of caution when it approves biosimilars. After all, one safety problem could stifle the industry's development. Moreover, the relatively low price discounts may be viewed as desirable for the biosimilar firms, and the experience in terms of market shares and sales in the EU is similar to that of specialty injectables and nonoriginal drugs in general. Therefore, the implications for biosimilars in the United States must be viewed cautiously.

Barriers to Market Entry

Biosimilars will encounter substantial barriers in their efforts to compete with branded biologics. These obstacles are more substantial than those encountered by small-molecule generics. Specifically, biosimilars have to overcome the particular barriers that are associated with manufacturing, marketing, storage (cold) and other distribution issues, delivery devices, immunogenicity (ie, patient adverse reactions because of live organisms), and special requirements for pharmacovigilance (ie, postsale monitoring).[2]

Complexity of Expertise

One of the major barriers is the complexity of manu-

facturing biologics and biosimilars. Companies with experience in manufacturing, especially in manufacturing biologics, such as Amgen and Biogen Idec, will have a considerable advantage over new companies with no such manufacturing experience. Therefore, experienced companies should dominate the market, which is one reason for the various alliances that enable these companies to be stronger competitors.

Biologics and biosimilars are sensitive to and altered by changes in their manufacturing process. The FDA must approve even minor changes in the production process. Achieving a sufficiently uniform product is difficult and costly even in different batches of the same product, which can make market entry risky and can discourage some potential entrants.[5] Manufacturing biosimilars, or biologics for that matter, requires scientific expertise and experience. There is a steep learning curve, which gives companies such as Amgen and Hospira an effective and substantial cost advantage.[5]

In 2009, Samsung announced a $389-million investment in biosimilars over 5 years.[13] Samsung believes that it has a competitive advantage in the manufacturing of biosimilars.[14] Giles Cottler, President of SAFC, stated, "existing larger biopharma players that are entering the biosimilar space, as well as continuing in the innovative space, probably have a better chance because of the complexity of the IP [intellectual property], the complexity of the processes, and the complexity of making a biosimilar."[15]

Large pharmaceutical companies will likely dominate the market, because they bring "marketing, sales, R&D, and manufacturing expertise to the table."[12]

Legal Issues

Other barriers to market entry involve legal factors, such as patents and trade secrets arising from the ACA. An official at a biologics and biosimilars company stated that the uncertainty is preventing companies without "deep pockets" from entering into the industry.[5]

The FDA has received 13 inquiries from companies considering possible biosimilar entry as of mid-January 2013, but no applications have been submitted; even after an application is submitted to the FDA, there is no guarantee that it will be approved.[16] There will be a considerable lag between application and approval. Therefore, the first biosimilar marketed in the United States may be at least several years away.

Lack of Automatic Substitution

The lack of essentially automatic substitution and interchangeability has helped make entry difficult for biosimilars. The generic market gained market share with automatic substitution at the pharmacy level. Other factors such as efforts by insurance companies were also important. Presently, 84% of the small-molecule chemical market consists of generic drugs, but it was a long process to achieve this market share.[17] It took some time for physicians and payers to accept generics, as will be the case for biosimilars.

The lack of identical products will make automatic substitution much more difficult to achieve for biosimilars. However, many biologics are administered by physicians; therefore, more emphasis will have to be directed at the physicians than was the case with small-molecule generics, thereby reducing the significance of automatic substitution to some extent. Greater biosimilar market shares should occur as physicians and patients become more familiar with them, in part because of the emphasis on decreasing healthcare costs.

Clinical Trials

Another barrier is the difficulty in attracting patients to clinical trials of biosimilars. Patients may be reluctant to participate in the trials, especially for serious diseases, because only some of them will receive the biosimilar rather than being confident of receiving the branded biologic outside of a clinical trial. A patient with breast cancer, for example, is unlikely to participate in a trial in which the choice is Herceptin or a biosimilar, which may or may not work.[18]

Because many companies may be attempting to develop the same biosimilar, it may be difficult to get enough volunteers because they are competing for the same limited population.[9] Based on discussions with people in the pharmaceutical industry, some biosimilar companies have encountered difficulties in obtaining the reference product for the trials, and when they do, it is often quite expensive.

Competition

Another factor leading to great risk is the uncertainty associated with other potential biologic or biosimilar competitors. For example, a study by the Biotechnology Information Institute reported that companies are working on 21 biosimilars and 12 biobetters for Herceptin and 21 biosimilars and 13 biobetters for Rituxan.[5] An approved biosimilar could therefore enjoy a large market share for a short time or perhaps not at all, because of the successful entry of another biosimilar or biobetter.

Also, the first entrant in the United States will not receive a 180-day exclusivity period that exists under the Hatch-Waxman Act for the first successful generic challenger, and the added cost of potential litigation may lead to a disadvantage for the first mover. A company could spend millions of dollars, only to find that its funds were wasted if a pioneer drug succeeds in obtaining a patent extension or a license for a biobetter.

Market Opportunities

Even given the uncertainty surrounding biosimilars, there are considerable commercial opportunities. The global sales of biologics amounted to $157 billion in 2011 and are estimated to reach more than $200 billion by 2016.[16] According to the IMS Institute for Healthcare Informatics, the US drug market shrank for the first time in 2012, but spending on specialty drugs (mostly biologics) increased by nearly 20%, and growth in this segment is forecasted to be 40% through 2014.[17] There are more than 45 monoclonal antibodies worldwide on the market, with revenues in excess of $40 billion.[19] There are currently no monoclonal antibody biosimilars marketed in the EU; however, 2 have received approval from the EMA, and marketing could begin in 2015, when their EU patent is expected to expire. Manufacturer SAFC estimates that approximately 860 biosimilars are in development.[15]

Biologics with estimated sales of $100 billion will come off patent by 2020.[20] Between 2009 and 2019, $50 billion of the market value of biologics in the United States alone will lose patent protection.[21] For example, Genentech is at risk of losing $10.7 billion in sales with patent expiration for Avastin, Herceptin, and Rituxan.[22]

Because it is easier to copy than create, biosimilars have a better chance to make it to market and are therefore less risky than branded biologics. In addition, the investment in biologics is much greater than in biosimilars, and the probability of success is lower. The R&D record of pharmaceutical companies shows that approximately 95% of all drug projects never make it to market.[23] The average cost of developing a new biotechnology drug as of December 2012 was estimated to be approximately $1.9 billion.[4] Furthermore, only 1 in 10 approved drugs become a commercial success, and the average time to obtain approval to market a drug is 13.5 years.[4] Only 9% of the drugs entering phase 1 clinical trials between 2004 and 2010 achieved regulatory approval, and only 22% of the biologic drugs entering phase 2 clinical trials have achieved approval.[4]

Because the market for many reference products is large, especially for monoclonal antibodies, there is an incentive for biosimilars to enter the market—a 5% share of a $1-billion market can lead to a good return on an investment: "Despite the inherent risk, biosimilars have the potential to exceed benchmark returns from any other form of R&D, a primary reason for increased alliances in the last 5 years."[21] Nevertheless, companies will need to spend considerably more on biosimilars than on small-molecule generics to enter the market; because they are not identical, presently no automatic substitution exists, and they must compete like a branded drug.[21] Furthermore, manufacturers must spend substantial sums to market the drug to physicians and to hospitals.

To the extent that the reference products have lower costs, as a result of economies of scale, the profit-maximizing strategy for the branded companies may well be to practice limit pricing; that is, price just high enough to deter the entry of biosimilars. However, to the extent that some originators' facilities are older and use outdated technology, their costs may be higher, and thus limit pricing would not work.

Because biosimilars are using newer technology, the cost of manufacturing them may be lower. Some biosimilars have been developed using plants, which can decrease their cost significantly. The Canadian company PlantForm has created a plant-based biosimilar version of Roche's Herceptin.[24] Because plants only require water and sunlight, PlantForm's manufacturing cost could be as much as 90% lower, and could result in a substantial decrease in price. Clinical trials for this biosimilar are expected to begin in 2014, and the launch is planned for 2016. Herceptin can cost as much as $100,000 annually per patient and has sales of more than $6 billion. Roche's patent runs out in 2014 in the EU and in 2017 in the United States. PlantForm is developing 2 additional biosimilar cancer drugs, which have global sales of more than $11 billion.[24]

In addition, monoclonal antibody biosimilars for palivizumab (Synagis) and rituximab were produced by using nontransgenic green plants. Illinois Biotechnology Industry Organization (iBIO) has developed the plant technology for rituximab, and its senior vice president believes that "the production of functional rituximab in plants suggests that many if not all monoclonal antibodies can be produced using the iBioLaunch system."[25]

Whether regulatory authorities would consider these plant-based products biosimilars, and whether these companies in the United States must go through the Biologics License Application (BLA) route instead of the abbreviated BLA (aBLA; ie, biosimilar) route is an issue that has to be decided. **Table 2** compares the application requirements for BLAs and aBLAs.

Companies of branded drugs may be reluctant to switch to entirely new technology, because it may be very difficult to get the biosimilar approved by the FDA as it was for its pioneer biologic. For example, Genzyme opened a new large plant in an attempt to produce Myozyme (alglucosidase alfa), but the FDA did not consider the product in the new plant to be the same as Myozyme.[26] Instead, Genzyme had to get approval from the FDA through a BLA for an entirely new biologic, Lumizyme (alglucosidase alfa), which was produced at the new plant. This resulted in a better biologic with new exclusivity.[27]

The cost of obtaining approval for biosimilars will decrease significantly if a new EMA guideline is passed

Table 2 Comparison of Biologics License Applications versus Biosimilars Applications

Drug application parameters	BLAs	aBLAs
Interchangeability	Not possible	Possible
Exclusivity period	Possible	Not possible
Patent licensing	Possible	Not possible
Sample size	Larger	Smaller
Proprietary data	Nondisclosure	Disclosure if challenged
Indications	Only indications for which it is approved by the regulatory agency	All indications of reference drug

aBLA indicates abbreviated Biologics License Application; BLA, Biologics License Application.

and is eventually adopted by the FDA. The EMA states that "with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an applicant to compare the biosimilar in certain clinical studies and in vivo nonclinical studies (where needed) with a non–EEA (European Economic Area)-authorized comparator (ie, a non–EEA-authorized version of the reference medicinal product) which will need to be authorized by a regulatory authority with similar scientific and regulatory standards as EMA (ie, ICH [International Conference on Harmonisation] countries)."[28]

If this is adopted by the EU and by the FDA, then all the biosimilars currently approved in the EU would potentially be automatically approved in the United States. The cost of biosimilar entry would decrease significantly when only 1 clinical trial is needed. The flip side of this is that easier market entry could lead to greater price discounts, which could reduce the incentives for R&D and innovation in the area of biosimilars.

Competitive Response

The reference product companies have not sat idly by, and have responded in different ways to the potential entry of biosimilars. They have followed strategies such as "improvements to the first-generation products, reducing the frequency of dosing schedules, and providing more convenient administration technologies [that] may extend patent protection" or achieve new exclusivity.[14] Other strategies include price decreases, patent defenses, and extensions, as well as the use of trade secrets.

Companies of branded drugs "are focusing on ways to expand and improve formulations, expression systems, dosing, delivery methods, and overall perception of superiority of branded innovator drugs over their biosimilar counterparts."[14] For example, Roche is developing a new subcutaneous formulation for MabThera that cuts treatment time from 2.5 hours to 5 minutes.[17] Another example is Amgen's first-generation epoetin alfa (Epogen), which has multiple weekly doses, whereas its second-generation epoetin alfa (Aranesp) has only weekly injections. This can improve healthcare outcomes, by improving patient adherence with once-weekly dosing.

Inherent in the risk of entering the biosimilar market is the possible extension of a patent. For example, Amgen was able to receive a 16-year patent extension on Enbrel (etanercept), which is now set to expire in the United States in October 2028. Therefore, companies that invested substantial amounts of R&D on an "Enbrel biosimilar" will not be able to recoup any return on their investment in the United States until at least 2028; given the constantly changing environment, those companies may never be able to get a return. Indeed, at a fairly modest 10% discount rate, $1 invested in 2012 will require more than $4 in net revenue in 2028. The EU patent for Enbrel is expected to expire in 2015.

Another important form of intellectual property is trade secrets. However, the BPCIA "may expose trade secrets of both originators and biosimilar applicants."[29] For example, there are "many aspects that could be kept as trade secrets, including precise cell growth conditions, analytical processes, purification process, and even characteristics of the cells that produce the drug."[26] Abbott has filed a citizen petition with the FDA, claiming that the BPCIA violates pharmaceutical companies' legal rights by forcing them to divulge trade secrets.[30] Abbott claims that "an innovator's resulting license application typically reflects more than a decade of research and contains analytical, preclinical, and clinical data, as well as detailed manufacturing information, most of which qualifies as trade secrets."[30] It further argues that even the federal government cannot try to control healthcare costs by taking private property.[30]

The claim is that branded companies should have reasonable expectations that their trade secrets will not be used to help their competitors.[31] If Abbott's claim is upheld, all biologics that were approved before the BPCIA was enacted would be exempt from the law, and no biosimilar will enter the United States until 2022.

The biotechnology companies AbbVie and InterMune have sued the EMA in an attempt to block publication of their clinical trial data.[32] AbbVie states that it "does not support the disclosure of commercially confidential information 'that does not meaningfully contribute to the scientific review or evaluation of products.'"[32] The General Court of the EU has issued an interim order that stops the EMA from releasing information on drugs from AbbVie and InterMune.[33] The issue concerns re-

leasing "commercially confidential information," and is similar to the trade secrets issues that are being challenged in the United States; however, this ruling in the EU only applies to the data of the 2 companies.[33]

Under US law, if a biosimilar attempts to enter and the innovator claims that its patent is infringed on, both the branded drug and the biosimilar may be required to reveal trade secrets.[30] This may also lead to antitrust issues. If trade secrets must be divulged, the result may be that pharmaceutical companies are less willing to spend R&D on life-saving innovative biologics.[30]

Roche decided to stay out of biosimilars and to focus on improved versions of patented medicines. Herceptin's patent expires in the EU in 2014 and in the United States in 2019.[14] The company developed 2 new drugs, Perjeta (pertuzumab) and Kadcyla (ado-trastuzumab emtansine), to replace Herceptin. The typical course of Perjeta costs $188,000.[18] And its new drug has recently shown good results—obinituzumab (GA101), which significantly decreased the risk of disease progression or death from chronic lymphocytic leukemia.[34] This could be the next-generation biosimilar for Rituxan; the FDA has designated it a breakthrough therapy and has given obinituzumab a priority review. This drug could be on the market before biosimilar competition for Rituxan arrives in a few years.[34]

Furthermore, some branded drug companies have responded in the market by lowering prices and creating second-generation biologics that are an improvement over the original agent and give the companies new patent and exclusivity rights. Branded biologics with annual sales of $1 billion to $2 billion and that are profitable will fight competition. For example, the price of Aranesp was cut when biosimilars entered the EU market.[35]

The availability of a superior second-generation biosimilar could significantly decrease the demand for an inferior first-generation biosimilar.[14] Also, the pricing of a second-generation biosimilar near that of a first-generation biosimilar could help the branded drug to control the market.[14] For example, Neulasta, a second-generation of Neupogen (filgrastim), has a single treatment cycle cost of $3400 compared with Neupogen's cost of $6000.[36] This is an approximate 40% cost reduction. Biosimilars could not compete with such a second generation if the biosimilar is priced only 30% less.

Biosimilar Developments

Uncertainty over the impending regulatory framework and defense strategies by branded drugs has caused delays and has prompted some companies to halt drug development.[37] Lonza is reviewing whether it is still worth investing in its biosimilar joint venture with Teva.[37] It suspended its late-stage trial for MabThera in October 2012. Lonza's chief executive Richard Ridinger stated, "I would like absolute clarity before we make a large investment. The quality of decisions is more important than speed."[37] He also states that the biosimilar development cost would exceed the $105.6 million that was estimated in 2009.[37]

Similarly, Merck, Teva, and Samsung have encountered severe setbacks and have suspended some biosimilar projects.[38] Jeff George, a division head of generics at Sandoz, states, "There are emerging signs of a shakeout in biosimilars and only the strong will survive." Richard Murray, PhD, vice president of Merck's biologics and vaccines unit added, "There has been a little bit of volatility."[38] Such a shakeout is common in the early days of an industry, but it indicates the risk involved.

Celltrion may be third in the race to develop a biosimilar for Rituxan.[39] It will finish a phase 1 trial before it revives its phase 3 trial, which it has altered after discussion with regulators.[40] Sandoz and Boehringer Ingelheim are already conducting phase 3 trials for biosimilars of Rituxan. Rituxan loses patent protection in the EU in 2013. Samsung and Teva have suspended their phase 3 trial.[40] Given the high cost of phase 3 clinical trials of biosimilars and the uncertain regulatory environment, the risk is so high that some companies are reluctant to proceed.

In 2013, Celltrion was seeking a major pharmaceutical company to buy a controlling interest from its chief executive officer, indicating that it may be having financial difficulties.[40] It recently received approval by the EMA for a Remicade biosimilar. Celltrion is aiming for approval of a biosimilar for Herceptin in Korea and in the EU. Its phase 3 trial is completed, but it has not filed for approval yet in the EU.[40]

Sandoz has 7 ongoing phase 3 studies across 5 biosimilar molecules.[12] Teva's Tevagrastim, a biosimilar for Neupogen, will be marketed in November 2013 as a biologic in the United States under an agreement with Amgen.[39] While defending its 12 biologics, Amgen is also entering the biosimilar industry with 6 biosimilars of its competitors.[41] Hospira "doesn't expect biosimilars to become key to its financial forecasts for at least 5 years."[35]

Humira (adalimumab) has more than 200 patents, and AbbVie will defend them all.[38] "You have scientific complexity but also patent attorneys that influence market."[16] Merck gave up its biosimilar project on Enbrel when Amgen got its expanded patent life.[38] Dr Murray of Merck stated that "its portfolio is shifting away from the copies."[16] Merck dissolved a dedicated biosimilar unit; however, it started over by forming a partnership with Samsung. Also, if Abbott prevails in the trade secret issue, the biosimilar market will not open in the United States until 2022. Companies may turn to the BLA instead of following the aBLA route.

BLA versus aBLA

In the United States, even though the FDA has the legal right to approve biosimilars, there are presently no approved guidelines established for an aBLA approval. Some companies may enter through the BLA route. Teva and its partner Lonza received FDA approval in 2012 for a BLA for tbo-filgrastim, which competes with Neupogen.[42] The same drug is a biosimilar in the EU under the name of Tevagrastim. Once the FDA opens the aBLA route, the choice will not be obvious, because there are advantages and disadvantages to each route.

A new biologic approved under the BLA would never get interchangeability, but it can be marketed as a competing brand, or even as a biobetter, which would get exclusivity and maybe even patent rights. Furthermore, "the difference in the amount of data the FDA requires under the 2 routes may be very small."[43] Even with the larger sample required for the BLA, the cost may be lower as a result of the company using only its product and not that of its competitors (which could be very costly). Unless the patent has expired, patent infringement issues are still valid; however, the company does not need to disclose proprietary data.[34]

The advantage of using the biosimilar route (ie, aBLA) allows the company to extrapolate and "piggyback" on the branded reference product, which will also get approval for all the indications for which the reference product is approved. The BLA can only be marketed for the indication for which the new biologic is approved. Therefore, if a product has only 1 indication, it may be better to use the BLA. However, with many indications, the better strategy may be a biosimilar. In addition, under the biosimilar route, the drug may eventually be able to be interchangeable and be substituted for the reference product, without having to perform comprehensive clinical trials. This cannot occur under the BLA.

Conclusions

The characteristics of biosimilars, along with the competitive aspects of the pharmaceutical industry, suggest that large, well-established companies will dominate the market. It is likely that alliances will continue to be prevalent to share the risk and uncertainty of biologic and biosimilar development. However, some companies have been successful by themselves.

The best strategy for a biosimilar entrant may be to enter emerging markets, which have lower entry barriers, to develop strong postmarketing data to show that the product is truly a biosimilar, and then to enter more stringently regulated areas with an established record. "Early market entry, state funding, and low costs make biosimilars an attractive opportunity in emerging markets and a rise of such products has been seen in these markets."[19] An added advantage is the less intellectual property protection, lower periods of exclusivity, and lower development and manufacturing costs in these markets, which could lead to 50% price reductions.[19] For example, Dr Reddy's strategy involves "Launching products in emerging markets 4 to 5 years ahead of the United States,"[22] which will allow it to gather data in India before entering the US market. Such economies associated with learning by doing will permit it to be a more effective competitor in developed markets.

The possibility of using plants to produce biologics could reduce prices substantially, leading to greater acceptance of biosimilars. The complexity of biosimilars requires substantial expertise for survival; it also explains why there are so many alliances. Smaller companies that may develop a biosimilar will probably need an established firm to sell it in developed markets. Brand names along with established companies may be necessary to overcome physician resistance. Automatic substitution may arise after some considerable time, as experience is gained with biosimilars, but because many biologics are administered by physicians, this issue may be less important than with small-molecule generics.

The business of biosimilars has not developed as quickly as expected. Despite all the current difficulties, it is expected that the market will develop, given the potential profits with patent expiration. Moreover, the mandate to decrease healthcare costs and to increase access to these life-saving pharmaceuticals will increase the biosimilar market. Appropriate public policy should encourage biosimilars but should also ensure that they are safe. The experience in the EU shows that biosimilars have been proved safe. Once the US market is open for biosimilars, regulatory and antitrust authorities should ensure that competition from biosimilars is allowed to develop, but also ensure that pioneer drug firms have sufficient incentives to develop new biologics. The 12-year market exclusivity is probably adequate. The biosimilar market will become more prominent, but this will take considerable time and effort. ■

Author Disclosure Statement

Dr Blackstone has reported no conflicts of interest. Dr Fuhr was on the expert stakeholder panel of NeoTract.

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STAKEHOLDER PERSPECTIVE

Modeling the Future Economic Impact of Biosimilars' Entry into the US Market

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RESEARCHERS: This comprehensive overview by Blackstone and Fuhr of the process and implications of how biosimilars may enter the US market should serve as the foundation for all future planning and thinking about the future direction of biosimilars. Using the experience from the European Union and coverage and utilization data from other industrialized countries, including reference pricing and reimportation, this article offers valuable insights into any future financial impact projections or modeling. Many of the current and future actions of the US Food and Drug Administration are well documented and are delineated by Blackstone and Fuhr, ranging from new requirements in clinical trials research to pharmacovigilance, establishing the reader's expectations of what hurdles will likely lay ahead of biosimilars in an attempt to mitigate the high cost of entry into the US market.

PAYERS: Many payers from both public and private organizations view biosimilars with mixed feelings. This profile of the barriers to biosimilars entering the US market outlined in this article, and what implications that may bring to both therapeutic pricing categories as well as to formulary selections, offers deeper insights into the multiple challenges facing the future use of biosimilars. The cautions suggested by the authors help to temper any expectations of a rapid uptake similar to small-molecule generic drugs, and paints a more sobering rate of approval and utilization resulting from multiple key factors, including safety, quality, manufacturing standards, substitution, and physician preference.

On balance, the opportunities that biosimilars can offer in helping to control costs within current therapeutic categories through more competitive pricing are clear. Lower-cost products, as pointed out, will likely improve the range of treatment options when making formulary selections, without necessarily overstretching already thin budgets. New and novel business practices may emerge that will help biosimilars find their footing, and may likely include emerging risk concepts agreements that target clinical outcomes, cost-effectiveness guarantees, and patient adherence measures.

PATIENTS: Patients may see the greatest impact of biosimilars as new products are introduced to a much wider international audience on a country-by-country basis. The greatest impact may come from novel manufacturing and distribution partnerships in third-world countries and to populations that are currently denied access to specialty drugs. Blackstone and Fuhr challenge the concept that biosimilars may discourage innovation, offering a small glimpse into what may drive a new business model for new product development and profit margins.

The challenge presented by the authors will inevitably evolve into improved pathways of reaching a much wider and diverse set of low-income patients and cultures, while at the same time successfully delivering care under the mandate of decreasing operating budgets and shrinking margins.